

A Case of von Hippel-Lindau Disease with Aortic Valve Insufficiency

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Von Hippel-Lindau (VHL) disease is an autosomal dominant hereditary disorder caused by a germline mutation of the VHL gene. It is a multi-systemic disorder that is predisposed to benign or malignant tumors of visceral organs such as hemangioblastoma of the central nervous system, renal cell carcinoma, retinal angioma and pheochromocytoma. We report herein a case of VHL disease that initially manifested with aortic valve insufficiency.

Key Words: von Hippel-Lindau disease, Aortic valve insufficiency

INTRODUCTION

Von Hippel-Lindau (VHL) disease is a rare genetic disease causing multisystemic hereditary neoplastic syndrome. It is most commonly complicated with cerebellar hemangioblastoma, retinal angioma, renal cell carcinoma (RCC), and pheochromocytoma.¹ Both the VHL disease and aortic valve insufficiency (AI) are uncommon diseases with reported incidence of AI from 0% to 33% within the general population.² The concurrent development of both AI and VHL disease is considered extremely rare. We report a case of the VHL disease that was initially manifested with typical symptoms of AI.

CASE

A 24-year-old female has been presented with progressive dyspnea and chest discomfort for the past 6 months. She was previously in a healthy condition with normal exercise capacity until the incidental diagnosis of hypertension two

years before the presentation. After the diagnosis of hypertension, she had not been treated nor had any further symptoms. Transthoracic echocardiography at the local clinic revealed significant AI and she was transferred for further evaluations. On presentation, vital signs showed the following: blood pressure of 150/70 mm Hg, pulse rate of 76/min, respiratory rate of 18/min and body temperature of 36.5°C. Heartbeats were regular and a high-pitched, decrescendo, grade III/VI diastolic murmur was audible at left lower sternal border. Her height was 172 cm, weighing 42 kg and her father died of metastatic RCC at 43 years old. Initial electrocardiogram was unremarkable and the routine blood chemistry also did not show any abnormalities. Transthoracic echocardiography disclosed severe AI with regurgitant volume of 68 cc per beat and regurgitant fraction of 54%. Left ventricle (LV) ejection fraction was approximately 50% and a diastolic internal dimension of LV was 60 mm (Fig. 1).

Surgical correction was planned for the management of AI. However, the chest discomfort was paroxysmal and accompanied with palpitation and sweating. Hormonal tests from collected urine were performed to exclude pheochromocytoma and 24 hours urinary vanillylmandelic acid and metanephrine was increased to 12.9 mg/day and 3.9 mg/day respectively. Following the abdominal contrast, enhanced computed tomography revealed not only both adrenal pheochromocytoma (Fig. 2A) but also multifocal masses in liver and

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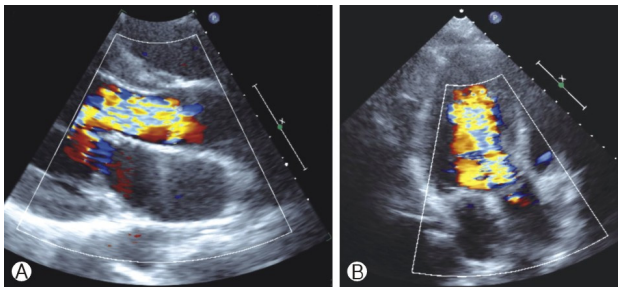


Fig. 1. Aortic valve insufficiency in transthoracic echocardiography. Parasternal long axis (A) and 3-chamber view (B) shows severe regurgitation of blood through the aortic valve. The estimated regurgitation volume was 68 cc and the regurgitation fraction was 54%.

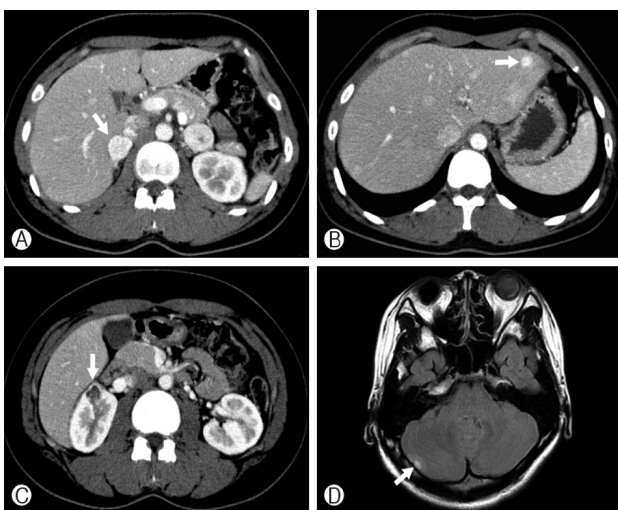


Fig. 2. Multifocal tumors in VHL disease. Contrast enhanced computed tomography shows well-enhanced both adrenal pheochromocytomas (A, white arrows), strong enhancing hepatic hemangioma in S2 segment of liver (B, white arrow) and right renal cell carcinoma (C, white arrow). T2 weighted brain magnetic resonance images show hemangioblastoma with peritumoral edema in cortical area of right cerebellum (D, white arrow).

kidney. A small enhancing mass in S2 segment of the liver was compatible with hemangioma (Fig. 2B) and both hypervascular renal masses were compatible with RCC (Fig. 2C). Multifocally developed uncommon tumors suggested the VHL disease. Magnetic resonance imaging (MRI) of the brain showed hemangioblastoma with ill-defined high signals in right cerebellum cortical area (Fig. 2D). In the ophthalmologic examination, left phthisis bulbi and right retinal hemangioma were being observed.

Setting aside the RCC history of her father, VHL disease was diagnosed with her hemangioma and multifocal visceral

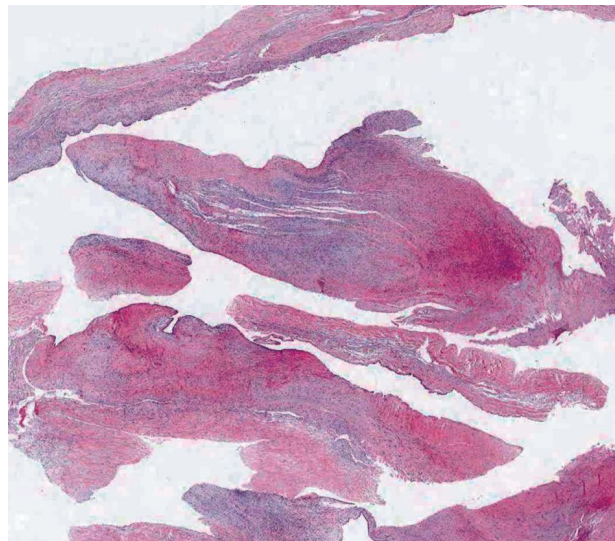


Fig. 3. Microscopic findings. The extracted aortic valve shows infiltration of lymphocytes with focal necrotic changes. There is no evidence of rheumatic valve disease (H&E stain, $\times 10$).

tumors. And the genetic study identified missense germline mutation of the eightieth codon and the sequencing of three exons of VHL gene by polymerase chain reaction.

A laparoscopic bilateral adrenalectomy with bilateral renal biopsies was followed by aortic valve replacement without any complications. Intraoperative renal biopsy revealed clear cell type RCC in the left kidney whereas biopsy from the right kidney showed no evidence of malignancy. Three fragments of the extracted aortic valves were thickened and retracted with focal yellowish degenerative changes showing chronic inflammation without evidence of rheumatic valve disease (Fig. 3).

The patient is being followed up periodically with abdominal computed tomography scans, which monitors the size of her renal mass. Until now, no neurological deficit has been detected.

DISCUSSION

VHL disease is an autosomal dominant cancer syndrome resulting from the mutation of the VHL gene, which is responsible for the proteolytic degradation of the hypoxia inducible factor (HIF) transcriptional complex. Abnormal or absent VHL protein function can disrupt tumor suppressions indirectly through HIF-mediated effects or directly through VHL-mediated effects, or both. Altered tumor suppressive

effects resulting from the degradation of HIF is known to cause various rare tumors.^{3,4}

Diagnosis of the VHL disease is made according to the following three criteria; one or more hemangioblastoma within the central nervous system, presence of visceral lesions (with the exception of epididymal and renal cysts, which are frequent in the general population), and familial incidence. Families with VHL disease are divided to several phenotypes. Families with type 1 VHL disease can develop all types of tumor except for pheochromocytoma. Families with type 2 VHL disease have pheochromocytoma and they are subdivided into three subtypes;^{1,3,5} type 2A have low risk for RCC, type 2B have high risk for RCC and type 2C have only pheochromocytoma and no other tumors of the VHL disease.^{3,6}

VHL disease causes various manifestations originating from multifocal tumors.^{1,5} In this case, the patient was being presented with typical symptoms of AI whereas the VHL disease was incidentally diagnosed while evaluating AI. Although the pheochromocytoma was functional with paroxysmal chest discomfort, palpitation and sweating, they were initially misread as symptoms of AI. It was essential to distinguish the symptoms of pheochromocytoma from the symptoms AI through the diagnosis of VHL disease.

The period in which the pheochromocytoma started developing within the patient is unclear. However, previous studies recommend regular screening of VHL tumors for the members of the VHL family as most VHL tumors develop between the ages of ten and forty, with the average age being about twenty six.⁷ The twenty-two years old patient in the presented case had progressive symptoms of AI for six months. Regarding her previous healthy conditions and the usual age of pheochromocytoma development in VHL disease, there may be a causal connection between the pheochromocytoma and subsequent development of AI. Although the direct relation between hypertension and AI is uncertain, it is known that hypertension can be a possible cause of AI.^{8,9}

However, the hemodynamic impact of functioning pheochromocytoma could have aggravated the AI which was clinically insignificant in the past.^{9,10} Because the patient did not have any cardiovascular symptoms and had normal ability to exercise in previous years, we carefully suppose that AI have been developed or worsened from the hemodynamically significant pheochromocytoma originated from VHL disease.

RCC in VHL disease is known to grow slowly. However,

the treatment option is limited to nephrectomy or radiofrequency ablation because RCC is refractory to medical treatments. In addition, nephrectomy or ablation is usually postponed until the manifestation of symptoms or significant increases in size because of its recurrence in most patients.¹¹ The proper timing for surgery has not been established and VHL disease patients with RCC are managed conservatively to reserve renal functions.^{11,12} They are at increased risks for end-stage renal disease.¹³ The patient in the presenting case is also being treated conservatively whereas the pheochromocytoma was managed with aggressive surgical resection.

Current guidelines recommend surgery for the patients with AI of low ejection fraction or LV enlargement.¹⁴ The patient in this case is presented with 6 months of progressive dyspnea. Regarding the New York Heart Association on classification II dyspnea and dilated LV with decreased ejection fraction, the best optimal treatment strategy is thought to be the surgery.

AI is an uncommon disease and the VHL disease is also rare. It is uncertain whether AI is associated with the VHL disease or has developed in isolation. However, considering the scarcity of both diseases, the concurrent development of AI in young ages and VHL disease which is also expected to be extremely rare suggests a possibility of temporal and causal relation between the two diseases. Hereby, we report a case of VHL disease which was initially manifested as typical symptoms of AI.

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